

<https://helda.helsinki.fi>

---

Conclusions about intervention effects should not be based on  
surrogate end points : [Letter]

Hemilä, Harri

2007

---

Hemilä , H 2007 , ' Conclusions about intervention effects should not be based on surrogate  
end points : [Letter] ' , Free Radical Biology & Medicine , vol. 42 , no. 4 , pp. 578-578 . <https://doi.org/10.1016/j.freeradbiomed.2006.11.035>

---

<http://hdl.handle.net/10138/228089>

<https://doi.org/10.1016/j.freeradbiomed.2006.11.035>

---

acceptedVersion

---

*Downloaded from Helda, University of Helsinki institutional repository.*

*This is an electronic reprint of the original article.*

*This reprint may differ from the original in pagination and typographic detail.*

*Please cite the original version.*

## Conclusions about intervention effects should not be based on surrogate end points [Letter to the Editor]

Hemilä H

Free Radical Biology and Medicine 2007; 42:578

Published version: <http://dx.doi.org/10.1016/j.freeradbiomed.2006.11.035>

Pre-print version of the manuscript

Harri Hemilä

Department of Public Health, POB 41

University of Helsinki,

FIN-00014

Finland

[harri.hemila@helsinki.fi](mailto:harri.hemila@helsinki.fi)

<http://www.ltdk.helsinki.fi/users/hemila>

Experts of controlled clinical trials argue that decisions on medical interventions should be based on clinically relevant outcomes and not on surrogates such as laboratory measurements. There are quite a few examples in which the effect on a surrogate end point substantially diverged from the effect on a clinically relevant outcome [1,2].

In this respect, the recent paper by Bruno *et al.* is problematic as it proposed higher vitamin E intakes for smokers on the basis of greater disappearance rate of  $\alpha$ -tocopherol in the plasma of smokers [3]. The disappearance rate is a surrogate end point with no validated relation to any clinically relevant outcome.

In our analyses of the ATBC Study cohort, we found that smoking modifies the effect of 50 mg/day vitamin E supplementation; however, the modification takes place in the direction opposite to that proposed by Bruno *et al.* In the  $\geq 72$ -year-old ATBC Study participants who smoked  $\geq 15$  cigarettes per day at baseline, vitamin E supplementation increased common cold incidence by 42% (95% CI: +18% to +70%), whereas in those who smoked less, vitamin E reduced common cold incidence by 29% (95% CI: -9% to -46%) [4].

Similarly, smoking modified the effect of vitamin E on pneumonia incidence. In the ATBC Study participants who had initiated smoking at later age, vitamin E reduced pneumonia incidence in those who quit smoking during the follow-up by 79% (95% CI: -40% to -93%), but had no effect on those who continued smoking (95% CI: -47% to +19%) [5].

Thus, in the case of these two respiratory infections, vitamin E supplementation appeared beneficial for those who were smoking less, but it was harmful or ineffective for those who smoked heavily at baseline or continued smoking during the follow-up. These findings with clinically relevant outcomes thus contradict the surrogate-based proposal by Bruno *et al.* that smokers would benefit of higher vitamin E intakes and it would seem necessary for them to consume at least 15 mg/day of vitamin E [3]. Furthermore, the current US RDA recommendation level for vitamin E, 15 mg/day, is not based on any clinically relevant outcome either and is arbitrary [6]. The divergence in the effects of vitamin E supplementation in the ATBC Study cohort indicates that caution should be maintained in any proposals that people should increase their consumption of vitamin E until its effects are better understood.

## References

- [1] Fleming, T. R.; DeMets, D. L.; Surrogate end points in clinical trials: are we being misled? *Ann. Intern. Med.* **125**:605-613; 1996. <http://www.annals.org/cgi/content/abstract/125/7/605>
- [2] Rothwell, P. M. External validity of randomised controlled trials: "To whom do the results of this trial apply?" *Lancet* **365**:82-93; 2005. [http://dx.doi.org/10.1016/S0140-6736\(04\)17670-8](http://dx.doi.org/10.1016/S0140-6736(04)17670-8)
- [3] Bruno, R. S.; Leonard, S. W.; Atkinson, J.; Montine, T. J.; Ramakrishnan, R.; Bray, T. M.; Traber, M. G. Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. *Free Radic. Biol. Med.* **40**:689-697; 2006. <http://dx.doi.org/10.1016/j.freeradbiomed.2005.10.051>
- [4] Hemilä, H.; Virtamo, J.; Albanes, D.; Kaprio, J. The effect of vitamin E on common cold incidence is modified by age, smoking and residential neighborhood. *J. Am. Coll. Nutr.* **25**:332-339; 2006. <http://dceg.cancer.gov/atbcstudy/pdfs/hemila253322006.pdf>
- [5] Hemilä, H.; Virtamo, J.; Albanes, D.; Kaprio, J. Vitamin E and beta-carotene supplementation and hospital-treated pneumonia incidence in male smokers. *Chest* **125**:557-565; 2004. <http://dx.doi.org/10.1378/chest.125.2.557>
- [6] Hemilä, H. Do vitamins C and E affect respiratory infections? [Dissertation] University of Helsinki, Helsinki, Finland; 2006: 67. Available at: <http://ethesis.helsinki.fi/julkaisut/laa/kansa/vk/hemila/>